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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
[illegible]	
ART UNIT	**PAPER NUMBER**
1656	8

DATE MAILED: 08/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/532,708	JAIN ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-51 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 11, 18, 25-33, 36-45, 48 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 11, 33 and 45 are indefinite because they do not clearly set forth the metes and bounds of the patent protection desired, being drawn to a robotic system comprising a large number of components and combinations thereof.

B) Claim 18 recites the limitation "said genomic DNA" in line 1. There is insufficient antecedent basis for this limitation in the claim.

C) Claim 25 is indefinite because the limitation of introducing target nucleic acid into embryo(s) or organism(s) using a robotic system is not supported by a description of how such introducing is accomplished.

D) Claim 26 is indefinite because the limitation of expressing target nucleic acid using a robotic system is not supported by a description of how the expressing is accomplished.

E) Claim 27 is indefinite because the limitation of identifying cell(s), embryo(s) or organism(s) with an altered phenotype using a robotic system is not supported by a description of how such identification is accomplished, especially taking into account the fact that a very large number of possible phenotypic changes have been described in the specification.

F) Claim 29 is indefinite because of the limitation of mapping expressed target nucleic acid using a robotic system. There is no description of the type of mapping procedure used and how it is performed using a robotic system.

G) Claim 30 recites the limitation "said altered phenotype" in line 1. There is insufficient antecedent basis for this limitation in the claim.

H) Claim 32 is indefinite because the limitation of identifying a bioactive agent which modulates the activity of the expressed target nucleic acid using a robotic system is not supported by a description of how such process is achieved using a robotic system.

I) Claim 39 is indefinite because the limitation of determining the haplotype is not supported by the description of what is meant by a haplotype and how it is determined.

J) Claim 48 is indefinite because of the limitation "target nucleic acid comprises a haplotype", since the haplotype is not defined in the specification.

K) Claim 49 recites the limitation "said genomic DNA library" in line 1. There is insufficient antecedent basis for this limitation in the claim.

L) Claims 36-44 are indefinite because the limitations of means for accomplishing the different functions by a robotic system are not described in the specification (see MPEP § 2185). In addition, the procedures such as DNA isolation, sequencing, haplotype determination, introduction of nucleic acids into cells, nucleic acid expression in cells, identifying altered phenotype in cells, identifying bioactive agents modulating biological activity of expressed nucleic acid can be performed in a variety of ways, some of which would not be amenable to automation.

MPEP § 2185 states:

If a "means or step plus function" limitation recited in a claim is not supported by corresponding structure, material or acts in the specification disclosure, the following rejections should be considered:

(A) under 35 U.S.C. 112, first paragraph, as not being supported by an enabling disclosure because the person skilled in the art would not know how to make and use the invention without a description of elements to perform the function. The description of an apparatus with block diagrams describing the function, but not the structure, of the apparatus is not fatal under the enablement requirement of 35 U.S.C. 112, first paragraph, as long as the structure is conventional and can be determined without an undue amount of experimentation. *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971);

(B) under 35 U.S.C. 112, second paragraph, as being indefinite. *In re Dossel,* 115 F.3d 942,946,42USPQ2d 1881, 1884 (Fed. Cir. 1997); and

(C) under 35 U.S.C. 102 or 103 where the prior art anticipates or renders obvious the claimed subject matter including the means or step that performs the function specified in the claim, the theory being that since there is no corresponding structure, etc., in the specification to limit the means or step plus function limitation, an equivalent is any element that performs the specified function.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 34-38 rejected under 35 U.S.C. 102(b) as being anticipated by Cathcart et al. (WO 91/16675).

A) Claim 34 is drawn to a robotic system comprising means for producing a plurality of enhanced homologous recombination (EHR) compositions. Claim 35 is drawn to a robotic system further comprising means for contacting the EHR compositions with a cellular library under conditions where the compositions hybridize to one or more target nucleic acids in the library. Claim 36 is drawn to a robotic system further comprising means for

isolating target nucleic acids. Claim 37 is drawn to a robotic system further comprising means for producing a library of mutant target nucleic acids. Claim 38 is drawn to a robotic system further comprising means for sequencing target nucleic acids.

B) The following descriptions were provided in the specification:

i) means for producing a plurality of enhanced homologous recombination (EHR) compositions and means for contacting the EHR compositions with a cellular library: robotic system with a thermocycler, cooling position, automated pipettor, positions for tubes and plates (page 34, lines 11-39, page 35, line 1-29).

ii) means for isolating target nucleic acids: robotic system with an automated pipettor, positions for tubes and plates (page 35, lines 24-39); lines 31-39 describe manual isolation of DNA.

iii) means for producing a library of mutant nucleic acids: the process, described on page 43, lines 1-14, involves making a plurality of EHRs using a pool of targetting polynucleotides, each of which contains one or more mismatches. There is no description of how this is accomplished by a robotic system, and means for EHR formation using a robotic system were described on pages 34-35 (see above).

iv) means for sequencing target nucleic acids: not described in the specification. Assuming standard dideoxynucleotide sequencing, a robotic system with a thermocycler, cooling position, automated pipettor, positions for tubes and plates would be sufficient.

Cathcart et al. teach an automated laboratory system comprising a liquid-handling instrument with a modular stations to support liquid containers, automated pipettor, heating and cooling stations, thermocycler and a magnetic separation station for performing DNA isolation, all

controlled by a computer system (Abstract; page 6, third paragraph; page 7; page 8, paragraphs 1 and 2; Fig. 1; page 10-15; page 23, paragraphs 3, 4; page 24; page 25, paragraphs 1 and 2).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 11, 12-18, 33, 47-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sena et al. (U.S. Patent No. 5,273,881) and Cathcart et al. (WO 91/16675).

A) Sena et al. teaches a method of detecting DNA target by:

1. providing a composition comprising a recombinase, a set of two DNA probes (polynucleotides) that each have sequences complementary to the target DNA and also contain a region of complementary overlap to each other, where the probes can be labeled for capture with biotin or digoxigenin (separation moiety),

2. contacting the composition with target DNA under conditions which permit hybridization of probes to target DNA,

3. detecting the complex containing the target DNA (col. 3, lines 40-63, col. 4, lines 31-33;).

The probe-target complex can be isolated by capturing the labeled probe on solid support (col. 4, lines 24-27) and can be used for isolation and enrichment of target DNA sequences (col. 23, lines 22-40). Target nucleic acids include DNA from a variety of organisms, and the detection can be for diagnostic purposes, such as diagnosis of infectious diseases, screening cells for the presence of other organisms, detection of gene mutations, deletions,

insertions, or rearrangements (col. 13, lines 63-67; col. 14, lines 1-27). This method can also be used for mapping genes or regulatory sequences in a chromosome (col. 20, lines 42-53).

B) Sena et al. do not teach performing the providing and contacting steps using a robotic system.

C) Cathcart et al. teach a robotic system for performing molecular biology procedures (see above).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the robotic system of Cathcart et al. in a method of Sena et al. with a reasonable expectation of success. The motivation to do so would have been that robotic system simultaneously processed a large number of samples.

7. Claims 5-6, 19-20, 25-27, 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sena et al. and Cathcart et al. as applied to claims 1 and 12 above, and further in view of Short (U.S. Patent No. 6,057,103).

A) Claims 5-6 and 19-20 are drawn to making a library of target nucleic acids, introducing it into a cellular library and performing phenotypic screening of the cellular library, wherein at least one of the steps uses a robotic system. Claims 25-27 and 29-30 are drawn to using a robotic system to introduce target nucleic acid into cells, express target nucleic acid and identify the altered phenotype due to the expressed target nucleic acid and mapping the expressed target nucleic acid. Claims 31 and 32 are drawn to using a robotic system to contact cells with a library of bioactive agents and identifying the bioactive agent.

B) Neither Sena et al. nor Cathcart et al. teach making and screening libraries of nucleic acids, expression screening or screening against bioactive agents.

C) Short teaches generation of expression libraries from isolated nucleic acids and screening such libraries by transferring the clones into cells and screening the cells (Abstract, col. 5, lines 26-35, lines 60-67). Gene libraries are generated by insertion of isolated DNA into a vector or plasmid (col. 9, lines 54-61). The library of clones is prepared by transforming suitable hosts with the vectors, and the resultant library is screened. Clones can be subjected to mutagenesis to generate variants (col. 19, lines 1-16). Screening can be performed on a mixture of clones (col. 14, lines 20-40).

The cells can then be exposed to potential drug candidates in drug discovery assays (col. 18, lines 40-49).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the methods of making and screening of clone libraries and cells taught by Short in the combined method of Sena et al. and Cathcart et al.. The motivation to do so, expressly provided by Short, would have been that there was a need for bioactive compounds with novel activities.

8. Claims 7-10 and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skena et al. and Cathcart et al. as applied to claim 12 above, and further in view of Ghai et al. (U.S. Patent No. 5,955,269).

A) Claims 7-10 and 21-24 are drawn to making cells comprising target nucleic acid, adding a library of agents to cells and determining the effect of these agents on cells using a robotic system for one of the steps, where the target nucleic acid is a gene sequence knock-out or knock-in, or comprises insertion, substitution or deletion.

B) Neither Skena et al. nor Cathcart et al. teach introducing target nucleic acid into cells and screening cells against bioactive agents.

C) Ghai et al. teach methods of screening for the presence of bioactive substances in food by testing for their ability to modify gene expression in cells in vitro (col. 2, lines 51-67) or in animal models (col. 3, lines 1-15). The assays measure expression of genes (col. 3, lines 66-67; col. 4, lines 1-12) or determine phenotypic changes in cells (col. 4, lines 33-39). Once the effects of the active compound have been determined, the compound can be isolated and purified (col. 4, lines 44-50).

Genes screened in the assay include disease-associated genes or unknown genes (col. 4, lines 58-67). The target genes or gene regulatory sequences can be obtained by standard molecular biology methods from procaryotic or eucaryotic cells, cloned into a vector, and introduced into cells, which are then used for screening. Test cells are screened for changes in gene expression associated with the bioactive compound (col. 12, lines 1-15).

The expression vectors introduced into cells may contain selectable marker genes (col. 14, lines 40-50). The effects of bioactive compounds can be tested in animals, including transgenic animals (col. 16, lines 7-10; lines 44-51). The cells can be cultured and assayed using a robotic device (col. 17, lines 18-30).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used the methods of Ghai et al. in a combined method of Sena et al. and Cathcart et al.. The motivation to do so, expressly provided by Ghai et al., would have been that a robotic system facilitated high throughput screening.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
August 21, 2001 TS

Kenneth R. Horlick, Ph.D.
KENNETH R. HORLICK
PRIMARY EXAMINER 8/21/01
GROUP 1600